



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-N-0908]

Agency Information Collection Activities; Proposed Collection; Comment Request; Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing an opportunity for public comment on the proposed collection of certain information by the Agency. Under the Paperwork Reduction Act of 1995 (the PRA), Federal Agencies are required to publish notice in the Federal Register concerning each proposed collection of information, including each proposed extension of an existing collection of information and to allow 60 days for public comment in response to the notice. This notice solicits comments on the collection of information concerning the establishment and operation of clinical trial data monitoring committees.

DATES: Submit either electronic or written comments on the collection of information by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Submit electronic comments on the collection of information to <http://www.regulations.gov>. Submit written comments on the collection of information to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: FDA PRA Staff, Office of Operations, Food and Drug Administration, 8455 Colesville Rd., COLE-14526, Silver Spring, MD 20993-0002, PRASStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: Under the PRA (44 U.S.C. 3501-3520), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal Agencies to provide a 60-day notice in the Federal Register concerning each proposed collection of information, including each proposed extension of an existing collection of information, before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality,

utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data
Monitoring Committees--(OMB Control Number 0910-0581)--Extension

Sponsors are required to monitor studies evaluating new drugs, biologics, and devices (21 CFR 312.50 and 312.56 for drugs and biologics, and 21 CFR 812.40 and 812.46 for devices).

Various individuals and groups play different roles in clinical trial monitoring. One such group is a data monitoring committee (DMC), appointed by a sponsor to evaluate the accumulating outcome data in some trials. A clinical trial DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. The DMC advises the sponsor regarding the continuing safety of current trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.

The guidance document referenced in this document is intended to assist sponsors of clinical trials in determining when a DMC is needed for monitoring a study, and how such committees should operate. The guidance addresses the roles, responsibilities, and operating procedures of DMCs, describes certain reporting and recordkeeping responsibilities, including the following: (1) Sponsor reporting to FDA on DMC recommendations related to safety; (2) standard operating procedures (SOPs) for DMCs; (3) DMC meeting records; (4) sponsor notification to the DMC regarding waivers; and (5) DMC reports based on meeting minutes to the sponsor.

1. Sponsor Reporting to FDA on DMC Recommendations Related to Safety

The requirement of the sponsor to report DMC recommendations related to serious adverse events in an expedited manner in clinical trials of new drugs (section 312.32(c) (21 CFR 312.32(c))) would not apply when the DMC recommendation is related to an excess of events not classifiable as serious. Nevertheless, the Agency recommends in the guidance that sponsors inform FDA about all recommendations related to the safety of the investigational product whether or not the adverse event in question meets the definition of “serious.”

2. SOPs for DMCs

In the guidance, FDA recommends that sponsors establish procedures to do the following things:

- Assess potential conflicts of interest of proposed DMC members;
- Ensure that those with serious conflicts of interest are not included in the DMC;
- Provide disclosure to all DMC members of any potential conflicts that are not thought to impede objectivity and, thus, would not preclude service on the DMC;
- Identify and disclose any concurrent service of any DMC member on other DMCs of the same, related, or competing products;
- Ensure separation, and designate a different statistician to advise on the management of the trial, if the primary trial statistician takes on the responsibility for interim analysis and reporting to the DMC; and
- Minimize the risks of bias that are associated with an arrangement under which the primary trial statistician takes on the responsibility for interim analysis and

reporting to the DMC, if it appears infeasible or highly impractical for any other statistician to take over responsibilities related to trial management.

3. DMC Meeting Records

The Agency recommends in the guidance that the DMC or the group preparing the interim reports to the DMC maintain all meeting records. This information should be submitted to FDA with the clinical study report (section 314.50(d)(5)(ii) (21 CFR 314.50(d)(5)(ii))).

4. Sponsor Notification to the DMC Regarding Waivers

The sponsor must report to FDA certain serious and unexpected adverse events in drugs and biologics trials (section 312.32) and unanticipated adverse device effects in the case of device trials (section 812.150(b)(1) (21 CFR 812.150(b)(1))). The Agency recommends in the guidance that sponsors notify DMCs about any waivers granted by FDA for expedited reporting of certain serious events.

5. DMC Reports of Meeting Minutes to the Sponsor

The Agency recommends in the guidance that DMCs should issue a written report to the sponsor based on the DMC meeting minutes. Reports to the sponsor should include only those data generally available to the sponsor. The sponsor may convey the relevant information in this report to other interested parties, such as study investigators. Meeting minutes or other information that include discussion of confidential data would not be provided to the sponsor.

Description of Respondents: The submission and data collection recommendations described in this document affect sponsors of clinical trials and DMCs.

Burden Estimate: Table 1 of this document provides the burden estimate of the annual reporting burden for the information to be submitted in accordance with the guidance. Table 2 of this document provides the burden estimate of the annual recordkeeping burden for the

information to be maintained in accordance with the guidance. Table 3 of this document provides the burden estimate of the annual third-party disclosure burden for the information to be submitted in accordance with the guidance.

Reporting, Recordkeeping, and Third-Party Disclosure Burdens: Based on information from FDA review divisions, FDA estimates there are approximately 740 clinical trials with DMCs regulated by the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and the Center for Devices and Radiological Health. FDA estimates that the average length of a clinical trial is 2 years, resulting in an annual estimate of 370 clinical trials. Because FDA has no information on which to project a change in the use of DMCs, FDA estimates that the number of clinical trials with DMCs will not change significantly. For purposes of this information collection, FDA estimates that each sponsor is responsible for approximately 10 trials, resulting in an estimated 37 sponsors that are affected by the guidance annually.

Based on information provided to FDA by sponsors that have typically used DMCs for the kinds of studies for which this guidance recommends them, FDA estimates that the majority of sponsors have already prepared SOPs for DMCs, and only a minimum amount of time is necessary to revise or update them for use for other clinical studies. FDA receives very few requests for waivers regarding expedited reporting of certain serious events; therefore, FDA has estimated one respondent per year to account for the rare instance a request may be made. Based on FDA's experience with clinical trials using DMCs, FDA estimates that the sponsor on average would issue two interim reports per clinical trial to the DMC. FDA estimates that the DMCs would hold two meetings per year per clinical trial resulting in the issuance of two DMC

reports of meeting minutes to the sponsor. One set of both of the meeting records should be maintained per clinical trial.

The “Average Burden per Response” and “Average Burden per Recordkeeping” are based on FDA’s experience with comparable recordkeeping and reporting provisions applicable to FDA regulated industry. The “Average Burden per Response” includes the time the respondent would spend reviewing, gathering, and preparing the information to be submitted to the DMC, FDA, or the sponsor. The “Average Burden per Recordkeeping” includes the time to record, gather, and maintain the information.

The information collection provisions in the guidance for 21 CFR 312.30, 312.32, 312.38, 312.55, and 312.56 have been approved under OMB Control No. 0910-0014; 21 CFR 314.50 has been approved under OMB Control No. 0910-0001; and 21 CFR 812.35 and 812.150 have been approved under OMB Control No. 0910-0078.

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden¹

| Section of Guidance/Reporting Activity | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Average Burden per Response | Total Hours |
|--|--------------------|---------------------------------|------------------------|-----------------------------|-------------|
| 5. Sponsor reporting to FDA on DMC recommendations related to safety | 37 | 1 | 37 | 0.50 (30 min.) | 18.5 |

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 2.--Estimated Annual Recordkeeping Burden¹

| Section of Guidance/Recordkeeping Activity | No. of Recordkeepers | No. of Records per Recordkeeper | Total Annual Records | Average Burden per Recordkeeping | Total Hours |
|--|----------------------|---------------------------------|----------------------|----------------------------------|-------------|
| 4.1. and 6.4 | 37 | 1 | 37 | 8 | 296 |

| | | | | | |
|---------------------------------|-----|---|-----|---|-------|
| SOPs for DMCs | | | | | |
| 4.4.3.2. DMC meeting records | 370 | 1 | 370 | 2 | 740 |
| Total | | | | | 1,036 |

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

Table 3.--Estimated Annual Third-Party Disclosure Burden¹

| Section of Guidance/Disclosure Activity | No. of Respondents | No. of Disclosures per Respondent | Total Annual Disclosures | Average Burden per Disclosure | Total Hours |
|---|--------------------|-----------------------------------|--------------------------|-------------------------------|-------------|
| 4.4.1.2. Sponsor notification to the DMC regarding waivers | 1 | 1 | 1 | 0.25 (15 minutes) | 0.25 |
| 4.4.3.2. DMC reports of meeting minutes to the sponsor | 370 | 2 | 740 | 1 | 740 |
| Total | | | | | 740.25 |

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

Dated: March 23, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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